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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/674,124	09/26/2003	Hidetoshi Inoko	WING-003CIP	2646
24353 7590 08/29/2007 BOZICEVIC, FIELD & FRANCIS LLP 1900 UNIVERSITY AVENUE SUITE 200 EAST PALO ALTO, CA 94303			EXAMINER KAPUSHOC, STEPHEN THOMAS	
			ART UNIT 1634	PAPER NUMBER
			MAIL DATE 08/29/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/674,124

Applicant(s)

INOKO ET AL.

Examiner

Stephen Kapushoc

Art Unit

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 January 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 5-20 is/are pending in the application.
- 4a) Of the above claim(s) 5-12 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 13-20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1-4 are cancelled.
Claims 5-20 are pending.
Claims 5-12 are withdrawn.
Claims 13-20 are examined on the merits.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/29/2007 has been entered.

This Office Action is in reply to Applicants' correspondence of 5/29/2007. Claim(s) 1-4 is/are cancelled; claim(s) 5-12 is/are withdrawn; claim(s) 20 has/have been newly added; claim(s) 8, 10, 11, 13, 14, 16-19 has/have been amended.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is **NON-FINAL**.

1. Please note, the text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Remarks: Restriction Requirement

2. The instant claims are drawn to methods for gene mapping comprising performing PCR using forward and reverse primers to amplify DNA sequences. The claims require using forward and reverse primers for each of the DNA sequences in a combination of DNA sequences comprising SEQ ID NO: 1-27,088. As such the claims require the analysis of each of the recited DNA sequences. As discussed in MPEP 803.04, the claims language of 'selecting a combination of DNA sequences comprising SEQ ID NO: 1-27,088', as recited in independent claim 13, requires a specific combination of sequences comprising the recited sequences. The claims are not drawn to any combinations comprising any subsets of the recited sequences.

Response to Remarks: Priority

3. As indicated (p.9 of Remarks) by Applicants, the priority document (JP 2002-383869) filed December 9, 2002 included a CD-ROM containing the sequence listing for SEQ ID NO: 1-27,088. The sequences are required for claims 13-20 of the instant application, and as such the effective filing date for the subject matter of those claims is December 9, 2002.

New Objections: Specification

4. The disclosure is objected to because of the following informalities:

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See ¶ 98 on page 19. Applicant is required to

delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The disclosure is objected to over recitation of the phrase 'from 2' – to 5' ', as recited in ¶ 218 on page 47, where likely 'from 3' – to 5' ' is intended.

The disclosure is objected to over recitation of the phrase '102 markers that have been identified as negative by the first screening' as recited in ¶ 244 on page 57, where ¶ 248 on page 60 indicates 'finding 102 markers positive'.

Appropriate corrections are required.

Withdrawn Claim Objections

5. The objection to claim 13 as set forth in the previous Office Action is **WITHDRAWN** in light of the amendments to that claim.

Withdrawn Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

6. The rejection of claims under 35 USC 112 2nd ¶ as indefinite as set forth in the previous Office Action is **WITHDRAWN** in light of the amendments to the claims.

New Claim Rejections - 35 USC § 112 1st ¶ - Description – New Matter

7. Claims 18 and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claims are drawn to methods in which a secondary screen is performed for the analysis of markers found positive through an initial screen, wherein the claims particularly require that method of the secondary screen comprises 'collecting DNA samples from descent groups'. There is not basis in the specification or claims as originally filed for the specific limitation of a secondary analysis with 'descent groups'. While the specification teaches analysis of positive markers in a secondary screen using the same subject group as the initial screen (p.48, ¶ 223) and analysis of positive markers in a secondary screen using the samples different from the samples of the initial screen (p.57, ¶ 244; p.19, ¶ 100), the specification does not specifically contemplate using samples that are different that are part of a descent group. And while the specification teaches the hereditary nature of diseases with a genetic component (e.g. p.17, ¶ 92), such a teaching is not sufficient basis for, or a particular contemplation of, a method in which a secondary screen comprising collecting DNA samples from a descent group is performed.

In conclusion, after an analysis of the requirements of the rejected claims, and the provisions of the originally filed specification and claims, the application does not have support for the limitation of 'collecting DNA samples from descent groups'.

8. The rejection of claims under 35 USC 101 as lacking utility is withdrawn in light of the requirements of the claims requiring a combination of DNA sequences comprising SEQ ID NO: 1-27,088, where the claims thus require the analysis of each of the 27,088 DNA sequences in the recited combination.

The instant disclosure provides examples of specific analyses using the microsatellite (MS) markers within SEQ ID NO: 1-27,088 to identify gene loci associated with psoriasis vulgaris, and rheumatoid arthritis. The specification teaches performing the claimed methods to identify a locus on the sixth chromosome that co-segregates with susceptibility for psoriasis vulgaris, which corresponds to conventional reports of this locus as associated with for psoriasis vulgaris (p.47 ¶ 218; p.56 ¶ 238). The specification further teaches performing the claimed method to identify positive MS association with the rheumatoid arthritis phenotype involving chromosome loci identified in the art as in significant linkage with the rheumatoid arthritis phenotype (p.58 ¶ 246). Given the specific results presented in the particular examples of the instant disclosure, the claimed method does have a specific, substantial, and credible utility at least in the identification of genomic loci that co-segregate with the susceptibility for the psoriasis vulgaris and rheumatoid arthritis phenotypes. Given that the instant claims require the analysis of each of SEQ ID NO: 1-27,088 the instantly claimed methods are commensurate in scope with the exemplified methods.

Withdrawn Claim Rejections - 35 USC § 112 1st ¶ - Enablement

9. The rejection of claims under 35 USC 112 1st ¶ for lack of enablement is withdrawn in light of the required limitations of the claims comprising 'collecting a combinations of DNA sequences comprising SEQ ID NO: 1-27,088' and performing PCR using DNA samples collected from subjects with forward and reverse primers where said primers are used for amplification of each of the recited DNA fragments.

New Claim Rejections - 35 USC § 112 1st ¶ - Scope of Enablement

10. Claims 13-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of identifying a DNA sequence fragment comprising a microsatellite in a human genomic region in which a gene associated with a phenotype exists, comprising:

selecting a combination of DNA sequences comprising SEQ ID NOs: 1-27,088, wherein each of the sequences comprises a microsatellite genetic polymorphism marker;

collecting DNA samples from subjects affected with said phenotype and control subjects not affected with said phenotype;

performing PCR on the DNA samples using forward primers consisting of 15-25 nucleotides wherein the forward primers consist of the same nucleotide sequence as the sequence extending in the 3'-direction from the 5'-terminus of each of the DNA sequences in said combination and reverse primers consisting of 15-25 nucleotides wherein the reverse primers consist of the sequence complementary to the sequence extending in the 5'-direction from the 3'-terminus of each of the DNA sequences in said combination to produce DNA sequence fragments, wherein each of said DNA sequence fragments comprises a microsatellite genetic polymorphism marker;

analyzing alleles of the microsatellite genetic polymorphism markers of said DNA sequence fragments; and

statistically comparing allele frequencies observed in the DNA sequence fragments produced from the affected subjects with those observed in the DNA sequence fragments produced from the control subjects to identify microsatellite polymorphism markers found positive whose allele frequencies observed in the DNA sequence fragments produced from the affected subjects are statistically significantly different from allele frequencies observed in their corresponding DNA sequence fragments produced from the control subjects, wherein the DNA sequence fragments

comprising at least one microsatellite polymorphism marker found positive are in a human genomic region in which a gene associated with a phenotype exists.

does not reasonably provide enablement for the analysis of any non-human subjects, or a gene mapping method comprising performing PCR using primers having a length up to 100 nucleotides or primers limited only by 'having a nucleotide sequence' complementary to the recited DNA sequences. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of the invention and breadth of the claims

The claims of the instant invention are drawn to gene mapping methods in which a particular combination of DNA sequences each comprising a polymorphic microsatellite (MS) marker is amplified, and there presence of particular variants within specific sequences is associated with a phenotype to identify a locus linked to the phenotype.

The claims encompass amplification of the 27,088 DNA sequences using the broadly claimed forward and reverse primers (as recited in claim 13, for example). The forward and reverse primers have lengths up to 100 nucleotides. The sequence required of any reverse primer is limited only in that it has 'a nucleotide sequence' complementary to the sequence of a DNA sequence in the required combination, where the indefinite article 'a' thus requires that the reverse primer minimally comprises only two contiguous nucleotides of the recited DNA sequences.

The claims thus encompass methods wherein an extremely broad and diverse collection of forward and reverse primers are used in a method that requires the specific amplification of each of SEQ ID NO: 1-27,088 as well as the analysis of variable MS content within each of the recited DNA sequences.

Direction provided by the specification and working example

The instant specification asserts that primers of various particular ranges in length may be used for the amplification of DNA segments that contain microsatellite markers (e.g.: p.45 ¶1212; p.35 ¶171). The specification further asserts that there are no limitations on a primer 'so long a it can amplify at least a portion of a target gene region' (p.35 ¶171).

The specification does not particularly identify any primers actually used for DNA amplification in the examples provided in the instant application (pages 44-60) by either primer structure (i.e. specific primer sequence) or other identifying characteristics (e.g. primer length and GC content).

The specification provides the sequences of 27,088 polymorphic DNA segments (i.e. SEQ ID NO: 1-27,088) throughout the human genome. The polymorphic DNA segments are diverse in their structure, with various sequences, lengths, and positioning of the polymorphic content. For example, analyzing only SEQ ID NO: 1-20, the segments range in size from 102 nucleotides to 466 nucleotides and include 7 segments under 200 nucleotides in length.

The instant specification does not provide any analysis of any non-human subjects.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art with regard to the amplification of any single nucleic acid sequence is high, the unpredictability associated with using primers as broadly claimed in the instant claims to amplify to required polymorphic content from 27,088 different DNA segments is even higher. There is also unpredictability in extrapolating the teachings of the instant specification to any non-human subjects.

Because the claims are not limited to human subjects, while the specification provides examples of only human analyses, and indicates that the DNA segments of SEQ ID NO: 1-27,088 are derived from the human genome, it is relevant to point out the differences in genomic sequences among different subject organisms. For example, Zhao et al (2004) teaches human, rat, and mouse genomic structure and sequence. It is thus unpredictable as to whether or not one might be able to use the method of the instant claims in the analysis of any non-human organisms.

Regarding the breadth of the claimed forward and reverse primers, it is relevant to point out that the claims specifically encompass primers up to 100 nucleotides in length. However, in a review of only the first 20 segments in the combination comprising SEQ ID NO: 1-27,088, it is noted that several segments are less than 200 nucleotides in length (i.e. SEQ ID NO: 4, 6, 7, 10, 14, 16, and 17 are 123, 102, 162, 142, 160, 163 and 183 nucleotides in length, respectively), and the specification provides not guidance as to where in any DNA segment the polymorphic nucleotide content is present. As such it is highly unpredictable as to how the primers in the full

scope of the claims would be successfully used in a gene mapping method. For example, given the 102 nucleotide DNA segment of SEQ ID NO: 6, if one were to use a 100 nucleotide forward primer and a 100 nucleotide reverse primer, one would not in fact amplify any nucleotide content in a manner suitable for associating MS alleles with a phenotype.

Further regarding the breadth of the claimed primers, considering the lack significant structural limitations of the primers (for example, see the analysis of the requirements of the reverse primers as detailed earlier in this rejection), and the requirement that the primers amplify specific genomic content as identified by SEQ ID NO: 1-27,088, it is relevant to point out the importance given to primer design in any amplification procedure. For example, Adb-Elsalam (2003) teaches the various parameters which need to be considered when designing primers for PCR, including length, melting temperature, and sequence (p.94). As such, it is unpredictable as to what primer sequences, other than primer sequences consisting of the sequences of the DNA segments of SEQ ID NO: 1-27,088 would in fact be suitable for the analysis of the polymorphic MS content in each of SEQ ID NO: 1-27,088, as required by the claims.

Quantity of experimentation required

A large and prohibitive amount of experimentation would be required to make and use the invention in the full scope of the claims. Such experimentation would require the analysis each of SEQ ID NO: 1-27,088 in any non-human organism to establish that in fact one can map any gene locus in any non-human organism using the

DNA segments as set forth in SEQ ID NO: 1-27,088. Furthermore, given the breadth of primers required for the claimed methods, and the fact that the polymorphic content within each DNA segment is not identified in the instant specification, one would be required to analyze a large amount of possible primers for the amplification of any one of the DNA segments as set forth in SEQ ID NO: 1-27,088 to determine what primers are in fact suitable for the analysis of polymorphic content in each segment.

Conclusion

After consideration of the teachings of the specification and the working examples, considering the breadth of the claims, and the unpredictability in the art, it is the conclusion that an undue amount of experimentation would be required to make and use the invention in the full scope of the claims.

Conclusion

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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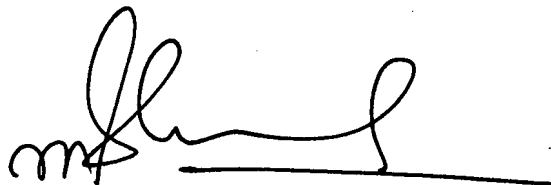
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Stephen Kapushoc
Art Unit 1634

A handwritten signature in black ink, appearing to read 'mshukla', is written over a horizontal line.

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER